Guidelines for the Use of Antiretroviral Agents in Pediatric HIV Infection

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Doravirine (DOR, Pifeltro) (Last updated April 16, 2019; last reviewed April 16, 2019)

For additional information, see Drugs@FDA: http://www.accessdata.fda.gov/scripts/cder/daf

Formulations

Tablet: 100 mg

Fixed-Dose Combination Tablet:

- [*Delstrigo*] Doravirine 100 mg/lamivudine 300 mg/tenofovir disoproxil fumarate (TDF) 300 mg

Dosing Recommendations

Child and Adolescent Dose:

- Doravirine is not approved for use in children or adolescents aged <18 years.

Adult (Aged ≥18 Years) Dose

Antiretroviral-Naive Patients:

- Doravirine 100 mg once daily

[*Delstrigo*] Doravirine/Lamivudine/TDF

Adult (Aged ≥18 Years) Dose:

- One tablet once daily

Selected Adverse Events

- Nausea
- Abdominal pain
- Diarrhea
- Abnormal dreams
- Insomnia, somnolence

Special Instructions

- Doravirine can be taken with or without food.
- Do not use doravirine with other non-nucleoside reverse transcriptase inhibitors.
- When doravirine is coadministered with rifabutin, the dose of doravirine should be increased to 100 mg twice daily. When doravirine/lamivudine/TDF (Delstrigo) is coadministered with rifabutin, an additional dose of freestanding doravirine (Pifeltro) needs to be administered approximately 12 hours later.
- Screen patients for hepatitis B virus (HBV) infection before using Delstrigo, which contains lamivudine and TDF. Severe acute exacerbation of HBV can occur when lamivudine or TDF is discontinued; therefore, hepatic function should be monitored for several months after halting therapy with lamivudine or TDF.
- See the lamivudine and TDF sections of the Drug Appendix for special instructions and additional information about the individual drug components of Delstrigo.

Metabolism/Elimination

- Doravirine is metabolized by the enzyme cytochrome P450 3A.

- Doravirine has multiple interactions with several drugs (see text below).

Doravirine Dosing in Patients with Hepatic Impairment:

- Dose adjustment is not required in patients with mild or moderate hepatic impairment. Doravirine has not been studied in patients with severe hepatic impairment.

Doravirine Dosing in Patients with Renal Impairment:

- Dose adjustment is not required when using doravirine in patients with mild, moderate, or severe renal impairment. Doravirine use has not been studied in patients with end-stage renal disease nor in patients on dialysis.
- Doravirine administered with lamivudine and TDF as components of Delstrigo **is not recommended** in patients with estimated creatinine clearance <50 mL/min.

Drug Interactions (see also the Adult and Adolescent Antiretroviral Guidelines and the HIV Drug Interaction Checker)

- Doravirine is a cytochrome P450 (CYP) 3A substrate that is associated with several important drug interactions with drugs that are strong CYP3A enzyme inducers. Coadministration with these drugs may cause significant decreases in doravirine plasma concentrations and potential decreases in efficacy and may lead to the development of resistance. Before doravirine is administered, a patient's medication profile should be carefully reviewed for potential drug interactions with doravirine.
- Doravirine **should not be coadministered** with the non-nucleoside reverse transcriptase inhibitors (NNRTIs) efavirenz, etravirine, and nevirapine.[1,2]
- Doravirine **should not be coadministered** with the following drugs: the anticonvulsants carbamazepine, oxcarbazepine, phenobarbital, and phenytoin; the androgen receptor inhibitor enzalutamide; the antimycobacterials rifampin and rifapentine; the cytotoxic agent mitotane; or St. John's wort.[1,2]
- Drug interactions between doravirine and rifabutin induce the metabolism of doravirine and require an additional doravirine 100 mg to be administered as a separate dose 12 hours apart.[1-3]

Major Toxicities

- *More common:* Nausea, headache, fatigue, diarrhea, abdominal pain, abnormal dreams.
- *Less common (more severe):* Neuropsychiatric adverse events, including insomnia, somnolence, dizziness, and altered sensorium. Immune reconstitution inflammatory syndrome may occur.

Resistance

The International Antiviral Society-USA (IAS-USA) maintains a list of updated resistance mutations and the Stanford University HIV Drug Resistance Database offers a discussion of each mutation. Doravirine is expected to have activity against HIV with isolated NNRTI resistance that is associated with substitutions

at positions 103, 181, or 190. However, some single mutations and combinations of the viral mutations have been shown to significantly decrease the susceptibility to doravirine. Specifically, clinical HIV isolates containing the Y188L substitution alone or in combinations with K103N or V106I; combination of V106A with G190A and F227L; or combination of E138K with Y181C and M230L, have shown ≥100-fold reduction in susceptibility to doravirine.[1,2] In patients with multiple NNRTI mutations, consult an HIV expert and a resistance database to evaluate the potential efficacy of doravirine.

Pediatric Use

Approval

Doravirine is not approved by the Food and Drug Administration for use in children or adolescents aged <18 years.

Efficacy in Clinical Trials

The efficacy of doravirine was evaluated using 48 weeks of data from two randomized, multicenter, double-blind, active controlled Phase 3 trials (DRIVE-FORWARD and DRIVE-AHEAD) that enrolled participants with HIV who had no history of antiretroviral treatment (N = 1,494).[4,5]

In DRIVE-FORWARD, adult subjects received either doravirine 100 mg (N = 383) or darunavir 800 mg plus ritonavir 100 mg (N = 383) once daily, each in combination with emtricitabine/tenofovir disoproxil fumarate (TDF) or abacavir/lamivudine. Eighty-four percent of patients who received doravirine and 80% of patients who received darunavir and ritonavir had HIV RNA <50 copies/mL at Week 48.[4]

In DRIVE-AHEAD, adult subjects received either coformulated doravirine/lamivudine/TDF (N = 364) or efavirenz/emtricitabine/TDF once daily (N = 364). Similar to DRIVE-FORWARD, 84% of participants who received doravirine/lamivudine/TDF and 81% of participants who received efavirenz/emtricitabine/TDF achieved virologic suppression (HIV RNA <50 copies/mL) at Week 48 of the DRIVE-AHEAD trial.[5]

Pharmacokinetics

The pharmacokinetics of doravirine have been evaluated in treatment-naive adults aged ≥18 years. A Phase 2 trial evaluated doravirine over a dose range of 0.25 times to 2 times the recommended dose of doravirine in treatment-naive participants with HIV who also received emtricitabine/TDF. No exposure-response relationship for efficacy was reported for doravirine.[5]

Toxicity

In the DRIVE-AHEAD clinical trial, 24% of participants who received coformulated doravirine/lamivudine/TDF and 57% of participants who received efavirenz/emtricitabine/TDF reported one or more neuropsychiatric adverse events.[5] Mild to moderate in severity adverse events were reported in 97% among the participants who received doravirine/lamivudine/TDF and in 96% of those who received efavirenz/emtricitabine/TDF. The majority of participants reported these events during the first 4 weeks of treatment in both groups. Neuropsychiatric adverse events led to treatment discontinuation for 1% of participants in both groups. At Week 48, the prevalence of neuropsychiatric adverse events was 12% in the doravirine/lamivudine/TDF group and 22% in the efavirenz/emtricitabine/TDF group.[5]

References

1. Doravirine/lamivudine/tenofovir disoproxil fumarate (Delstrigo) [package insert]. 2018. Food and Drug Administration. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/210807s000lbl.pdf.
2. Doravirine [package insert]. Food and Drug Administration. 2018. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/210806s000lbl.pdf.
3. Khalilieh SG, Yee KL, Sanchez RI, et al. Multiple doses of rifabutin reduce exposure of doravirine in healthy subjects. *J Clin Pharmacol*. 2018. Available at: https://www.ncbi.nlm.nih.gov/pubmed/29723418.

4. Molina JM, Squires K, Sax PE, et al. Doravirine versus ritonavir-boosted darunavir in antiretroviral-naive adults with HIV-1 (DRIVE-FORWARD): 48-week results of a randomised, double-blind, phase 3, non-inferiority trial. *Lancet HIV*. 2018;5(5):e211-e220. Available at: https://www.ncbi.nlm.nih.gov/pubmed/29592840.

5. Orkin C, Squires KE, Molina JM, et al. Doravirine/lamivudine/tenofovir disoproxil fumarate is non-inferior to efavirenz/emtricitabine/tenofovir disoproxil fumarate in treatment-naive adults with human immunodeficiency virus-1 Infection: week 48 results of the DRIVE-AHEAD Trial. *Clin Infect Dis*. 2018. Available at: https://www.ncbi.nlm.nih.gov/pubmed/30184165.